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Late gadolinium enhancement and adverse outcomes in a contemporary cohort of adult survivors of Tetralogy of Fallot

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Objective:

Myocardial fibrosis has been associated with poorer outcomes in Tetralogy of Fallot, however only a handful of studies have assessed its significance in the current era. Our aim was to quantify the amount of late gadolinium enhancement in both the LV and RV in a contemporary cohort of adults with surgically repaired Tetralogy of Fallot, and assess the relationship with adverse clinical outcomes.

Design:

Single centre cohort study

Setting:

National tertiary referral centre

Patients:

114 patients with surgically repaired Tetralogy of Fallot with median age 29.5 years (range 17.5 to 64.2). Prospective follow-up for mean 2.4 years (SD 1.29).

Interventions:

Cardiovascular magnetic resonance was performed, and late gadolinium enhancement mass was estimated for the LV using the 5-SD remote myocardium method, and for the RV using a segmental scoring system. Cohort characterisation was determined through the use of a computerised database.

Outcome measures:

Survival analysis from time of scan to first adverse event, defined as an episode of atrial arrhythmia, sustained ventricular arrhythmia, hospitalisation with heart failure, or implantable cardioverter-defibrillator insertion.

Results:

11 patients experienced an adverse outcome in the follow-up period, although there were no deaths. LV late gadolinium enhancement was associated with adverse outcomes in a univariate model ($p = 0.027$). However, when adjusted for age at scan the significant variables included NYHA class ($p = 0.006$), peak oxygen uptake ($p = 0.028$), number of prior sternotomies ($p = 0.044$), and higher indexed RV and LV end diastolic volumes ($p = 0.002$ and $p < 0.001$), but not RV or LV late gadolinium enhancement.

Conclusions:

Formal quantification of late gadolinium enhancement is not currently as helpful in ascertaining prognosis compared to other, more easily assessed parameters in a contemporary cohort of Tetralogy of Fallot survivors, however assessment particularly of the LV holds promise for the future.

Introduction:

Tetralogy of Fallot (ToF) is the commonest cyanotic congenital heart defect with a reported birth prevalence of 0.34 per 1000 live births worldwide¹. With improvements in surgical technique and perioperative care survival into adulthood has improved dramatically, to the extent that over 95% of patients will survive to their 18th birthday²⁻⁴. However, despite the improvements in perioperative mortality, morbidity remains high. The principal adverse outcomes include arrhythmia (either supraventricular or ventricular), the need for repeat surgical or percutaneous intervention to treat residual haemodynamic lesions (e.g. pulmonary regurgitation or branch pulmonary artery stenosis), and heart failure. Of all of these sustained ventricular arrhythmia is the most devastating, as it may present as sudden cardiac death (SCD). The electrophysiological mechanisms behind this are likely to be multifactorial, with a combination of scar-related macro re-entry, ventricular dilatation, and ventricular fibrosis over time⁵⁻⁷.

Identifying patients who are most at risk of these complications is challenging, and so it is sometimes difficult to make precise recommendations regarding which patients should be followed up most intensively, or when to offer therapy such as an implantable cardioverter-defibrillator (ICD). Cardiac Magnetic Resonance (CMR) is now regarded as the gold standard for the serial non-invasive assessment of patients with ToF as it provides detailed and reproducible information on the structure and function of the heart post surgical repair. Amongst the parameters derived from this modality, it has been suggested that the presence and extent of late gadolinium enhancement (LGE) is associated with a greater risk of adverse outcomes in these patients⁸. However, these data relate to older ToF patients perhaps with less perioperative myocardial protection during repair. Whilst there has recently been interest in the use of T1 mapping to calculate extracellular volume fraction (ECV) as a marker of myocardial fibrosis in these patients⁹⁻¹², we could identify no studies which assessed the utility of formally quantifying LV LGE mass in the current era, unlike in other, acquired, cardiac diseases. The aim of this study was to quantify the amount of RV and LV LGE in adult survivors of ToF in a contemporary cohort, and establish its utility in identifying those patients at greater risk of adverse clinical endpoints.

Methods:

This was a prospective single centre cohort study. Since 2004 a national cardiac service for the provision of care to those patients with adult congenital heart disease (ACHD) has been established in Scotland, serving patients from a total population of 5.3 million. All surgical and catheter-based interventions, advanced imaging and functional testing have been delivered through a single centre since 2009, and a computerised database capturing outcomes for all adult patients exists. Information from the database was corroborated with electronic or paper based records, including the original operation notes where these were available. The primary care physicians were contacted where necessary. Baseline demographics included date of birth, gender, details of surgical repair including palliation, and date of death or last review. Morbidity outcomes documented were atrial arrhythmia (defined as sustained atrial tachycardia, supraventricular tachycardia, atrial flutter, or atrial fibrillation), clinically significant ventricular arrhythmia (defined as sustained ventricular tachycardia or ventricular fibrillation), the need for cardiac device insertion (permanent pacemaker or implantable cardioverter-defibrillator), and the need for percutaneous or cardiac surgical reintervention. Information on functional status included NYHA class and parameters derived from ECG, echocardiography, CMR and cardiopulmonary exercise testing (CPET).

All CMR scans were performed at the host institution at 1.5 Tesla field strength using a Siemens Magnetom Avanto (Siemens AG, Erlangen, Germany) with a 12-element phased array cardiac surface coil. A standard imaging protocol was followed for cases. Briefly, steady state free precession images in the following long axis planes were acquired: vertical long axis (LV 2 chamber), horizontal long axis (LV 4 chamber), LV outflow tract (LV 3 chamber), aortic arch, RV outflow tract in two orthogonal planes, RV 2 chamber, and RV inflow-outflow (RV 3 chamber views). A short axis stack of 10mm slices through the left and right ventricles from base to apex was also obtained. Settings were as follows: echo time/repetition time/flip angle was 1.4/3.5/50 with spatial resolution of 1.7 x 2mm. To assess function of the aortic and pulmonary valves phase-contrast velocity encoded flow mapping was performed in through-plane short axis views during breath holding, with an appropriate velocity envelope selected (generally up to 100 cm/s for a low velocity regurgitant jet). Late gadolinium enhancement (LGE) images were obtained 10-15 minutes after the administration of 0.15mmol/kg of Gadolenic acid (Dotarem®). The entire LV and RV were imaged using a phase sensitive inversion recovery sequence in contiguous short axis views from the level of the AV valves to the apex, and then in long axis views¹³. LV and RV volumes at end diastole and end systole were quantified using computer assisted planimetry and indexed to body surface area by a single analyst with over 5 years of CMR experience (HW). Pulmonary regurgitant fraction was calculated as a percentage of regurgitant volume divided by RV stroke volume on the flow-mapping sequences. LV LGE was formally quantified as late gadolinium mass and expressed as a percentage of the total LV mass using the 5 SD from remote myocardium method as previously described by our group¹³. The degree of RV LGE was expressed using the semiquantitative RV seven segment model proposed by Babu-Naryan and colleagues, and expressed as a score out of 20 (Figure 2)⁸.

Cardiopulmonary exercise testing was performed on a bicycle ergometer with a progressive 10-20 Watt per minute incremental workload to a symptom-limited maximum. Heart rate and rhythm were established using continuous electrocardiographic recording, blood pressure was measured non-invasively using brachial cuff sphygmomanometry (unless the patient had bilateral BT shunts; in the case of a unilateral BT shunt the contralateral arm was used), and tidal volume, respiratory rate, oxygen consumption and carbon dioxide output measured via respiratory spectrometry. Peak VO₂ was defined as the highest recorded value of VO₂ obtained during the last minute of exercise, and expressed as the peak predicted value of VO₂ for that patient according to the data from Jones and colleagues¹⁴. The VE/VCO₂ slope was derived from linear regression throughout the period of exercise testing. Peak heart rate was expressed as a percentage of the predicted maximum according to the equation 220 - age.

Statistical analysis was performed using IBM SPSS statistics version 22 (IBM corporation, Armonk, New York), and the analysis of the data consisted of two parts. The first was a cross-sectional analysis of the cohort at the end of the study period. The T test and Z test were used to compare means and distributions for normally distributed variables, and the Mann-Whitney U test was employed to compare ranks and medians for non-parametric data. Correlation for normally distributed data was assessed using the Pearson product-moment correlation coefficient, and the Spearman rank correlation coefficient if non-normal. Tests of association between nominal and continuous data were performed using one way ANOVA or the Kruskal Wallis test according to whether the distribution of the data was normal or non-normal.

The second part of the analysis involved comparison of survival curves for each baseline variable from the date of CMR scan to the end of the follow-up period. This was initially undertaken using a univariate Cox regression model from the date of CMR scan.

Because of the low number of adverse events over the follow-up period we decided to use a composite outcome of death, atrial

arrhythmia, sustained ventricular arrhythmia, ICD implantation or heart failure admission. We did not include PVR in this composite outcome as the threshold for deciding to perform this procedure varies according to many different factors, and this would have been extremely difficult to account for in a formal statistical analysis. If a baseline variable was associated with a greater risk of the composite outcome in the univariate model to a level of significance of $p < 0.2$, it was decided to repeat the analysis with age at the time of scan as a covariate in order to adjust for the effect of older age on the likelihood of experiencing an adverse event - the reasons for this became apparent during the course of the study and are outlined below. Due to the relatively low number of adverse outcomes it was not possible to use more than two covariates in the model.

Results:

At the time of data collection there were 376 adult survivors of tetralogy of Fallot known to our centre (male to female ratio 59:41). Of those patients 239 had undergone CMR scanning, and 118 of these had contrast enhanced CMR with the administration of gadolinium as gadolenic acid (Dotarem®), with 114 scans of sufficient quality to include in the final analysis (Figure 1). Characterisation of the cohort at the end of the study period is presented in table 1. The majority of patients were male and had the classical form of ToF. Approximately 40% of patients had received a palliative shunt prior to complete repair. Symptomatic dyspnoea was rare, with almost 95% of patients enjoying NYHA class 1 status.

Regarding outcomes there were no deaths or confirmed episodes of ventricular fibrillation. A total of 21 patients experienced an adverse outcome (table 2). There were 15 patients who experienced a sustained atrial arrhythmia, 4 patients who experienced an episode of sustained ventricular tachycardia, 3 patients who had a hospital admission with heart failure, and 6 patients who underwent implantation of an ICD. Four of the ICDs were secondary preventative devices following the development of sustained VT, and of the two primary preventative devices one was implanted on the basis of previous syncope and a high burden of NSVT on ambulatory ECG monitoring, and the other was implanted due to biventricular failure with LVEF less than 35% on optimal medical therapy as well as impaired RV systolic function.

Mean peak VO₂ was only mildly reduced at 70% predicted. VE/VCO₂ slope values were elevated, and the mean maximal heart rate was 82% of predicted, implying a degree of chronotropic incompetence for these patients. Regarding CMR data, the median indexed RV volumes were elevated in comparison to published ranges in healthy volunteers¹⁵. Median LVEDVi was comparable to published ranges in healthy volunteers however LVESVi was increased resulting in a slight reduction in ejection fraction. There was a bimodal distribution of the pulmonary regurgitant fraction. Approximately 22% of patients had negligible pulmonary regurgitation (RF <5%), either due to prior PVR which still retained good function, or an initial surgical repair which preserved the function of the pulmonary valve. The remainder (88%) had significant pulmonary regurgitation resulting in a median regurgitant fraction of almost 30%. All patients had at least some RV LGE evident. Median RV LGE score was 6/20, and the pattern of LGE was consistent, being almost always seen at the surgical sites of the RVOT and VSD patch, and the insertion points of the RV on to the LV. It was rare to see LGE elsewhere (Figure 3). Median LV LGE mass expressed as a percentage of total LV myocardial mass was low at 1.75%, and in almost all cases LGE was confined to in or around the insertion points of the RV on the interventricular septum. Only 9 patients had no LV LGE evident. There were three patients with overall significantly higher LGE mass than the remainder of the cohort. Two were confirmed as myocardial infarcts (one subendocardial, one transmural) presenting with acute coronary syndrome and undergoing coronary angiography demonstrating coronary artery occlusion consistent with supply to the myocardial territory affected, the other was a suspected 'silent' myocardial infarction and did not ultimately undergo angiography. These patients were removed from the analysis of LV LGE mass as outliers.

There was a statistically significant difference between the RV LGE score and age at scan ($p = <0.001$), and age at repair ($p = 0.044$). There was also a statistically significant difference between the LV LGE mass and age at scan ($p = 0.046$), and age at repair ($p = 0.040$). The Tukey post-hoc test was carried out to assess differences between groups and the results are outlined in figure 4. We also assessed the association between era of surgery and amount of RV and LV LGE. There was a significant difference between the amount of RV LGE in earlier and later cohorts ($p = 0.01$) but not LV LGE ($p = 0.394$).

The Spearman rank coefficient was used to identify whether there was any correlation between parameters derived from CMR and from CPET. There was no significant correlation between either RV LGE score and LV LGE mass and the following variables: peak VO₂, peak VO₂ as a percentage of the peak predicted value, VE/VCO₂ slope, and peak HR as a percentage of the peak predicted value. There was weak negative but significant correlation between RV LGE score and RVEF ($r = -0.193$, $p=0.036$). LV LGE score and LVEDVi were weakly correlated ($r = 0.216$, $p=0.021$), as were LV LGE score and LVESVi ($r = 0.201$, $p=0.032$). RV LGE score and LV LGE mass weakly correlated with each other ($r = 0.267$, $p=0.004$).

We then compared the characteristics of the 21 patients who experienced an adverse event (atrial arrhythmia, sustained ventricular arrhythmia, ICD implantation or heart failure admission) with the 93 patients who did not (table 1). The patients who had experienced an adverse event were significantly older both at age of repair and age at CMR scan. They were more likely to have symptomatic breathlessness, have a wider QRS duration on ECG, and have a higher VE/VCO₂ ratio on CPET. The RVEDVi and RVESVi were significantly higher as was LVESVi, although LVEDVi did not quite approach statistical significance. Consequently LVEF (but not

RVEF) was lower in this group. They displayed a higher LV LGE mass, and there was the suggestion that they also had a higher RV LGE score, although this did not reach significance at the 0.05 level.

As demonstrated in table 3 we used univariate regression to establish which factors were associated with an increased hazard of a composite outcome of adverse cardiac events at a mean follow up of 2.35 years (SD 1.29) from time of scan. A higher RVEDVi, LVEDVi, older age at scan, NYHA class, and LV LGE mass conferred risk for an adverse event, as did a lower RVEF, LVEF and peak HR during CPET (expressed as a percentage of the peak predicted value). Of note RV LGE score did not. Because we had already shown how the patients who experienced adverse events tended to be significantly older than those who did not, we decided to repeat the analysis adjusting for age at scan as a covariate, and the results are shown in table 4. Briefly, RVEDVi, LVEDVi, RVEF, LVEF and NYHA class all continued to be significantly associated to the development of adverse outcomes, as well as having a higher number of redo sternotomies or a lower peak VO2 during CPET. LV LGE mass and peak HR as a percentage of the predicted value during CPET trended towards but did not reach statistical significance at the 0.05 level.

Discussion:

In one of the largest CMR studies yet of adult survivors of surgical repair of ToF we characterised systematically the quantity and distribution of LGE within the right and left ventricles. We established the factors associated with increased LGE in each ventricle, and the utility of LGE as a marker of future adverse clinical outcomes.

The amount of LGE seen in the RV was relatively low in most patients, and almost exclusively consigned to the insertion points of the RV on to the LV, and sites of surgical intervention, namely the RVOT and site of VSD patch repair. This is similar to that reported previously⁸, and suggests that that myocardial fibrosis is either a direct consequence of surgery, or due to increased haemodynamic stress in the case of the RV insertion points. With the exception of a small number of outliers who had suffered myocardial infarcts the amount of LV LGE was also low with a median value of 1.75% (IQR 0.7 - 3.23%).

There was a weak relationship between the quantity of RV LGE seen and older age at surgery, older age at time of scan, and repair in an earlier surgical era. There was also a weak relationship between the LV LGE mass, and age at the time of scan and age at repair. These findings are perhaps not unexpected. Patients who underwent surgical repair in the 1960s and 1970s typically underwent repair of the defects through right ventriculotomy, and did not benefit from more modern techniques of myocardial preservation. From the 1980s onwards the preferred technique for repair was a combined transatrial and transpulmonary approach, with no direct incision over the free wall of the RV. This suggests that ventricular fibrosis may be associated with transventricular approach and earlier techniques of myocardial protection.

There was a weak but significant inverse correlation between RV LGE and RVEF, implying that increased fibrosis of the RV is associated with reduced stroke volume and RV systolic impairment. On the other hand, regarding the LV, whilst there was a positive correlation between LV LGE and indexed LV end diastolic volume, no corresponding inverse correlation between LV LGE and LVEF was seen. This perhaps suggests that LV fibrosis may be associated with an increase in LV end diastolic volume initially, with an increase in end systolic volumes and reduction in LVEF occurring later on, i.e. too late to be seen in our cohort over the specified follow-up period. Further work would be required to confirm this hypothesis, although it is well documented that LV dysfunction is typically a very late complication in repaired ToF¹⁶, and, as a relatively young cohort, our study population may therefore have been too "healthy" to display this relationship in its entirety. The overall impression of all of the above however, is that the amount of LGE is associated with a more dysfunctional ventricle, and this reinforces findings from previous work^{17,18}.

Interestingly however there was no significant correlation between LGE and adverse markers of exercise performance. This is likely to be because the determinants of exercise performance in individuals with repaired ToF are complex, depending not just on ventricular volumes and contractility - which could conceivably be affected by LGE as a marker of ventricular fibrosis - but also factors such as heart rate response, minute ventilation, and abnormalities of gas exchange. Furthermore, we were unable to adjust for baseline levels of training and fitness in individuals in this cohort, and so varying degrees of physical deconditioning may also have had an effect. Thus LGE in isolation is not particularly useful in this regard.

LV LGE mass, but not RV LGE score, was predictive of an adverse outcome over the follow-up period at the 0.05 level in a univariate model (Table 3), and interestingly this finding has been also shown by other groups when assessing myocardial fibrosis via the quantification of ECV: Chen and colleagues found that in a group of 84 ToF survivors greater LV ECV, but not RV ECV, was associated with arrhythmia on univariate analysis, although arrhythmia in this context included not just atrial arrhythmia and sustained VT but also frequent ventricular ectopy and non-sustained VT¹⁰. Broberg and colleagues looked exclusively at LV ECV in a smaller, older group of 48 ToF survivors, and over a follow-up period of 3.5 +/- 1.5 years reported that of the patients with extensive LV ECV (defined as a fraction >30%), 5/15 experienced the adverse outcome of atrial arrhythmia (3) or death (2), whereas only 2/37 patients experienced atrial arrhythmia in the low LV ECV group, with no deaths¹¹. The reason that RV LGE score, and indeed RV ECV, have not been shown to be predictive of an adverse outcome is unclear. It may well relate to the difficulty of assessing the thin-walled RV to the same degree of precision as the LV at 1.5 Tesla, furthermore the free wall of the RV in these patients is frequently adjacent to sternal wires, resulting in the problem of metallic artefact.

One key issue to bear in mind however is that when a bivariate analysis was performed, adjusting for age at the time of initial surgical repair, LV LGE mass trended towards but did not quite reach the 0.05 level of significance as a predictor of an adverse clinical outcome (Table 4). This is in contrast to other, more established makers of a poor prognosis in repaired ToF such as indexed RVEDV, LVEF, NYHA class and peak oxygen uptake on cardiopulmonary exercise testing which did achieve this level of statistical significance in our cohort. Overall this would suggest that more data is required, with larger cohorts, longer follow-up and more

adverse events, before the routine quantification of myocardial fibrosis can be recommended as a marker of prognosis or indeed studied with respect to its utility as helping to define thresholds for a clinical intervention.

When interpreting these findings a number of limiting factors need to be taken into account. This was a single centre study and included a heterogeneous group of patients. Despite being larger than other published studies of ToF patients undergoing CMR, our cohort was still relatively small and patients experienced a low number of primary outcome events, preventing multivariable analysis. Patients who had already received a pacemaker before they could undergo CMR scanning were by definition excluded, and they could well have been in a higher risk group, thus giving rise to selection bias. The semiquantitative means of estimating RV LGE is likely to be inferior to a formal quantification of RV LGE mass, although as described previously the latter is technically more difficult to achieve. Due to the method of estimating LV LGE mass from the short axis stack it was not possible to quantify any areas of LGE at the apex of the LV, as exemplified by some older patients who underwent insertion of a transmural apical vent at the time of surgery - however the amount of LGE here was likely to be negligible in terms of absolute quantity. Finally we did not repeat the administration of gadolinium contrast in follow up scans for the vast majority of patients, and so were unable to determine whether the amount of LGE increases over time and whether rate of change is more significant than the absolute value. However, given the small amounts of LGE seen overall, it is likely that a large time interval would be required to see any significant difference. We had to exclude patients who had already experienced an adverse outcome at the time of scan from the survival analysis; therefore as with other, similar, studies, our data is subject to the problem of left censoring.

In summary, in a contemporary cohort of patients with repaired ToF the amount of LGE is lower in younger patients who underwent repair at an earlier age. LGE is rarely seen outwith the sites of surgical repair or the insertion points of the RV on to the LV. It is associated with other markers of ventricular dysfunction such as increased volume and reduced ejection fraction, but not exercise performance. Our data suggest that LV myocardial fibrosis as quantified by LGE is useful as a univariate predictor of adverse outcomes in contemporary adult survivors of ToF. However the data does not allow the construction of a robust multivariable model, and in view of the low incidence of hard clinical endpoints in this patient group, it is clear that only a large, prospective, multicentre study with follow up for a much longer period of time will achieve this. If this data can be obtained then the risk of ventricular arrhythmia, heart failure hospitalisation, and death can be more formally quantified, thus helping to guide clinical decision making and perhaps allow the creation of a formal risk scoring system.

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Table legends:

- Table 1: Characteristics of cohort and differences between those who had any adverse event by the time of data collection and those who did not
- Table 2: Summary of adverse events at end of follow-up period. Note some patients experienced more than one adverse event, hence 28 events in 21 patients.
- Table 3: Prediction of a composite endpoint of atrial arrhythmia, sustained ventricular tachycardia, device insertion, or hospitalisation with heart failure after index CMR scan
- Table 4: Prediction of a composite endpoint of atrial arrhythmia, sustained ventricular tachycardia, device insertion, or hospitalisation with heart failure after index CMR scan, adjusting for age at scan as a covariate

Figure legends:

- Figure 1: Determination of the study cohort
- Figure 2: Scoring system to semiquantitatively estimate the degree of RV LGE
- Figure 3: Distribution of RV LGE scores for all 114 patients in cohort
- Figure 4: Distribution of RV and LV LGE by age at scan and age at repair